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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FOSTER, CHRISTINE E	
ART UNIT	**PAPER NUMBER**
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/507,498	REGINSTER ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *10-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/13/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

1. Applicant's reply of 6/20/07 to the Notice of Non-Compliant Amendment is acknowledged. As correctly pointed out by Applicant, the Notice was in error. Applicant's amendment of 5/4/07 is acknowledged and has been entered.

2. The objection to the oath has been withdrawn in response to the Supplemental Declaration filed 5/4/07 listing the address of inventor Christgau.

Election/Restrictions

3. Applicant's election with traverse of Group I, claims 1-9 in the reply filed on 5/4/07 is acknowledged. The traversal is on the ground(s) that the groups of claims I and II are related to a single general inventive concept that represents a contribution over the prior art (Reply, pages 15-17). In particular, Applicant argues that Holmdahl reference relates to three polypeptides in a triple helix formation, while the binding partner described in the present invention cannot recognize the epitope HRGYPGLDG in triple helicoidal structure (see especially the Reply at page 16, the first and second paragraphs).

4. This is not found persuasive because the claims are not limited to immunological binding partners that only recognize HRGYPGLDG in the unwound form of collagen. Claim 1 fails to recite any limitation that would convey that the epitope is in a specific structure. Accordingly, Applicant's arguments that the Holmdahl reference is distinguished from the present invention on this basis are not persuasive since such features are not required by the independent claims.

5. Applicant's Reply further includes a discussion of "Coll2-2" (Reply, page 16, the second paragraph). However, no description of this molecule is provided or was found in the instant

specification. It is also unclear how such remarks are relevant to the instant restriction requirement. Applicant appears to argue unexpected results ("...probably increase discriminative power...") but this allegation cannot be correlated with the instant claims, which do not refer to Coll 2-2.

6. Applicant further argues that the binding partner of Holmdahl is capable of binding to the triple polypeptide complex and not the linear sequence of SEQ ID NO:22 (Reply, page 16, the third paragraph). This is not found persuasive because as above, there is nothing recited in the claims that requires that the epitope sequence be linear. Furthermore, Applicant has not provided any data or pointed to any teaching in the reference to support this analysis. Absent further elaboration, the arguments of counsel cannot be taken as evidence. MPEP 2145.

7. Similarly, the arguments that the binding partner of Holmdahl et al. cannot bind SEQ ID NO:1 (Reply, page 16, the fourth paragraph) are unsupported by evidence or clear scientific reasoning and are therefore interpreted as opinion testimony.

The requirement is still deemed proper and is therefore made FINAL.

8. Claims 10-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5/4/07.

Priority

9. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or

more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

It is noted that the oath refers to U.S. provisional application No. 60/363,926, filed 3/13/2002. If applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 119(e), **a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet.** For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications.

If the instant application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an

unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Specification

10. The specification is objected to because required subject headings, e.g. the "BACKGROUND OF THE INVENTION", "BRIEF SUMMARY OF THE INVENTION", and "BRIEF DESCRIPTION OF THE DRAWINGS" are not present.

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

11. The abstract of the disclosure is objected to because the word "utilizes" is misspelled in line 4.

Information Disclosure Statement

12. Applicant's Information Disclosure Statement filed 1/13/2005 has been received and entered into the application. The references therein have been considered by the examiner as indicated on the attached form PTO-1449.

13. Applicant is reminded that the listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter

later claimed. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." MPEP 2163.

In the instant case, the claims are drawn to a method of assaying **collagen type II or fragments thereof** using an "immunological binding partner" that is immunoreactive with an epitope comprised in the amino acid sequence HRGYPGLDG. This would encompass detection of collagen type II itself, i.e., collagen type II in the native form (wound or triple-helix collagen).

However, the specification makes clear that the immunological binding partner (antisera) of the invention did not in fact recognize the native or wound form of collagen.

The specification discloses that the antisera were raised against synthetic peptides having the sequence HRGYPGLDG (SEQ ID NO:1) conjugated to BSA (see Example 1). When tested for specificity, the antisera recognized the synthetic peptide HRGYPGLDG, but did not recognize native collagen type II (Example 2).

The specification clearly discloses that "[antiserum] Coll2-1 D3 does not bind native (wound) collagen type II" (see p. 16, lines 9-14).

Applicant has also argued on the record that "the binding partner describes [sic] in the present invention can not recognize the epitope HRGYPGLDG in triple helicoidal structure" (Reply of 5/4/07 at page 16, the first paragraph).

As such, with respect to claims 1-2 and 4-9, one skilled in the art cannot envisage possession of methods and kits for assaying *native or wound collagen type II* using the antiserum

of the invention, because Applicant specifically discloses that the antiserum is unable to recognize native or wound collagen type II. Similarly, Applicant has only described how to detect **fragments** of collagen type II that are *in the unwound form.*

Applicant's postfiling work also teaches that the HRGYPGLDG (SEQ ID NO:1) sequence "**is detectable only in its linear form released from collagen type II by proteolysis**" (Deberg et al., "One-year increase of Coll 2-1, a new marker of type II collagen degradation, in urine is highly predictive of radiological OA progression" *Osteoarthritis and Cartilage* (2005) **13**, 1059-1065, see especially at p. 1063, left column. Thus, Applicant's postfiling work indicates that the HRGYPGLDG (SEQ ID NO:1) sequence is a neoepitope that is not present in the native, wound form of type II collagen, but is only exposed upon proteolysis of type II collagen into unwound fragments.

In describing only antiserum that recognizes the neoepitope HRGYPGLDG (SEQ ID NO:1) sequence, Applicant has not described methods of detecting native, wound type II collagen since this neoepitope is not found in the native, wound form, and therefore this sequence would not be accessible for recognition by antiserum directed against this sequence. Similarly, Applicant has also not described methods of detecting all fragments of collagen type II since fragments that still retain the triple-helix or wound conformation would not contain the neoepitope HRGYPGLDG (SEQ ID NO:1) sequence.

16. Claims 1-9 also lack written description because the claims encompass detection of **all fragments** of collagen type II. However, in disclosing an antiserum raised against the sequence HRGYPGLDG (SEQ ID NO:1), the specification has only described how to detect collagen type

II fragments *that have this sequence*, since only fragments that include this sequence are capable of being recognized by the antiserum. One skilled in the art cannot envisage methods of detecting all possible fragments of collagen type II, since not all fragments would include the epitope recognized by antiserum of the invention. Although Applicant has identified the antibody epitope by reference to the sequence HRGYPGLDG (SEQ ID NO:1), the claims fail to recite that the fragments detected have this sequence, and therefore, Applicant has not described any partial structure that would be shared among members of the genus of fragments detected.

17. Claims 1-9 refer to an "**immunological binding partner**" that is immunoreactive with an epitope comprised in the sequence HRGYPGLDG (SEQ ID NO:1). However, the disclosure of *antibodies* (see for example p. 5, lines 24-27), coupled with the disclosure of methods of making such antibodies (see p. 9-10), fails to convey evidence of possession of the genus of *immunological binding partners* absent any disclosure of common partial structure, or physical and/or chemical properties shared by members of the genus.

One skilled in the art may reasonably envisage possession of immunological binding partner that are *antibodies* based on the disclosure of the antibody epitope HRGYPGLDG (SEQ ID NO:1) coupled with the knowledge in the art about how to produce antibodies against a known antigen.

However, Applicant has not adequately described the instantly claimed genus since there is no disclosure of any methods of making immunological binding partners other than antibodies. There is no specific disclosure of any immunological binding partners apart from antibodies. Although the genus is identified by reference to a functional characteristic (ability to recognize a

specific epitope), Applicant has not disclosed any correlation between structure and function, i.e., has not identified any structure that would be responsible for conveying this specific binding function. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

18. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for assaying *fragments of collagen type II that are in the unwound form and that comprise the sequence HRGYPGLDG (SEQ ID NO:1)*, does not reasonably provide enablement for assaying native, wound collagen type II or for assaying all fragments thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The nature of the invention is drawn to the production of antisera that recognize an epitope within the sequence HRGYPGLDG (SEQ ID NO:1), and the use of such antisera in detection of fragments of collagen type II produced by proteolysis. The specification discloses that such antisera were produced by immunization of rabbits with a synthetic peptide (HRGYPGLDG, SEQ ID NO:1) (see Example 1).

Claims 1-9 are drawn to methods for assaying **collagen type II or fragments thereof** using an "immunological binding partner" that is immunoreactive with an epitope comprised in the amino acid sequence HRGYPGLDG. Claims 13-16 are drawn to kits for performing the assay method of claim 1. Thus, the claims encompass using the antisera of the invention to detect

type II collagen or any fragment thereof. The claims also encompass not only antisera or antibodies, but any "immunological binding partner" that is specific an epitope within the SEQ ID NO:1 sequence.

However, with respect to claims 1-2 and 4-9, the specification clearly fails to teach the skilled artisan how to detect the native or wound (triple-helix) form of collagen type II. Rather, the specification repeatedly makes clear that the immunological binding partner (antisera) of the invention did not in fact recognize the native or wound form of collagen.

In particular, the specification discloses that when tested for specificity, the antisera recognized the synthetic peptide HRGYPGLDG, but did not recognize native collagen type II (Example 2). The specification clearly discloses that "[antiserum] Coll2-1 D3 does not bind native (wound) collagen type II" (see p. 16, lines 9-14).

Applicant has also argued on the record that "the binding partner describes [sic] in the present invention can not recognize the epitope HRGYPGLDG in triple helicoidal structure" (Reply of 5/4/07 at page 16, the first paragraph).

The specification provides no direction or guidance regarding how to assay *native or wound collagen type II* using the antiserum of the invention, because Applicant specifically discloses that the antiserum is unable to recognize native or wound collagen type II. Similarly, Applicant has only described how to detect **fragments** of collagen type II that are *in the unwound form*. There are also no working examples in which either the native, wound form of collagen type II, or fragments thereof having the wound conformation, were actually assayed.

Applicant's postfiling work teaches that the HRGYPGLDG (SEQ ID NO:1) sequence "**is detectable only in its linear form released from collagen type II by proteolysis**" (Deberg et

al., "One-year increase of Coll 2-1, a new marker of type II collagen degradation, in urine is highly predictive of radiological OA progression" *Osteoarthritis and Cartilage* (2005) **13**, 1059-1065, see especially at p. 1063, left column. Thus, Applicant's postfiling work indicates that the HRGYPGLDG (SEQ ID NO:1) sequence is a neoepitope that is not present in the native, wound form of type II collagen, but is only exposed upon proteolysis of type II collagen into unwound fragments.

As such, in describing only antiserum that recognize the neoepitope HRGYPGLDG (SEQ ID NO:1) sequence, the specification fails to teach how to detect native, wound type II collagen since this neoepitope is not found in the native, wound form, and therefore this sequence would not be accessible for recognition by antiserum directed against this sequence. Similarly, the specification fails to teach how to detect all fragments of collagen type II since fragments that still retain the triple-helix or wound conformation would not contain the neoepitope HRGYPGLDG (SEQ ID NO:1) sequence. One skilled in the art would have no expectation of success in employing antibodies that recognize epitopes within the HRGYPGLDG (SEQ ID NO:1) sequence to detect native, wound collagen type II or fragments thereof that are in the wound conformation, since this epitope is only exposed upon proteolysis of collagen type II into linear fragments.

Since Applicant's postfiling work teaches that this epitope can only be detected in linear fragments, and not in the native, wound form of collagen, it would clearly represent an undue burden of experimentation to attempt to detect native, wound collagen and fragments thereof in the wound conformation using an antibody directed against an epitope that is not present in the wound conformation.

The claims are also broadly directed to detection of collagen type II or **any** fragments thereof. This would include fragments that include the HRGYPGLDG (SEQ ID NO:1) sequence as well as those that do not. Such a genus is clearly characterized by substantial variability, in that it includes fragments of any length that may be non-overlapping and have no amino acids in common with each other. The specification, in teaching antibodies directed against the HRGYPGLDG (SEQ ID NO:1) sequence, only teaches how to detect fragments that include this sequence, i.e., those fragments that have the epitope recognized by the antibody of the invention. The specification is entirely devoid of guidance with respect to detecting fragments that do not contain the antibody epitope, and therefore fails to predictably enable one skilled in the art to carry out the claimed invention with respect to assay of **any** fragments of collagen type II.

19. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "immunological binding partners" that are **antibodies**, does not reasonably provide enablement for all "immunological binding partners". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to an "**immunological binding partner**" that is immunoreactive with an epitope comprised in the sequence HRGYPGLDG (SEQ ID NO:1), and to methods and kits for using such an immunological binding partner for assaying collagen type II or fragments thereof.

The specification discloses that "immunological binding partners" include polyclonal, monoclonal, or humanized antibodies (p. 5, lines 24-27), but does not provide a limiting

definition for this term, such that the claims are not limited to "immunological binding partners" that are antibodies.

The specification provides guidance with respect to production of antibodies having specificity for the sequence HRGYPGLDG (SEQ ID NO:1). In particular, the specification outlines art-recognized methods of raising antibodies against synthetic peptides having this sequence (see p. 9-10). The specification also discloses working examples in which antisera were raised in this manner.

However, the specification fails to provide any guidance or direction with regard to producing "immunological binding partners" other than antibodies. There are no working examples in which "immunological binding partners" other than antibodies were actually produced.

Therefore, due to the lack of direction/guidance presented in the specification regarding how to make immunological binding partners other than antibodies, the lack of working examples directed to same, and in light of the breadth of the claims, the specification fails to teach the skilled artisan how to make and use the claimed invention in its full scope without undue experimentation.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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